REMARKS

Response To Restriction Requirement And Claim Amendment

Claims 16, 18-29 and 43, 45-55, as amended, and new claims 79 and 80 are pending in this application. As set forth pages 2-3 of the Office Action, the Examiner required restriction of the present application to one of five inventions designated Groups I-V. Applicants elect, with traverse, Group II, which includes claims 16-29 and 43-55, drawn to methods of treating nicotine addiction and smoking cessation, for prosecution in this application. As a result of the restriction requirement and the election, claims 1-15, 30-42 and 56-78 have been canceled without prejudice. Applicants expressly reserve the right to prosecute any canceled or unclaimed subject matter in one or more continuation, divisional, or continuation-in-part application(s).

Claims 16, 18, 19, 23-29, 43, 45, 47, and 50-55 have been amended to more particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claims 17 and 44 have been canceled without prejudice. New claims 79 and 80 have been added to recite specific features in the original claim 45. Support for the amendments can be found in the specification at, *e.g.*, page 16, lines 27-36. Since no new matter has been introduced by these amendments, Applicants respectfully request their entry into the records of the present application.

Rejection of Claims 16-29 and 43-55 Under 35 U.S.C. § 112 is Obviated

As set forth on pages 3-4 of the Office Action, claims 16-29 and 43-55 were rejected under 35 U.S.C. § 112 as allegedly being indefinite and failing to particularly point out and distinctly claim the subject matter of the invention. This rejection has been either obviated by the amendments, *i.e.*, the cancellation, without prejudice, of claims 17 and 44, or overcome for reasons as set forth below.

The Examiner alleged that "It is not clear how much (+)-stereoisomer the recitation 'substantially free of its (+)-stereoisomer' is intended to exclude and the specification does not define this." Applicants respectfully submit that the term "substantially free of the (+)-stereoisomer" is fully and clearly defined in the specification.

See, e.g., specification at page 13, line 27 to page 14, line 12. The specification not only provides Applicants' definition of the term, but also delineate the term with several examples and preferred embodiments. *Id.* Applicants respectfully submit that one of ordinary skill in the art, based the disclosure, would know what is meant by the term. *See, MPEP* § 2173.05(b); *Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819 (Fed. Cir. 1988).

For the above reasons, Applicants submit that the rejection under 35 U.S.C. § 112, second paragraph, has been obviated or overcome and respectfully request that the rejection be withdrawn.

Rejection of Claims 16-29 and 43-55 Under 35 U.S.C. § 103(a) Should Be Withdrawn

As set forth on pages 4-5 of the Office Action, claims 16-29 and 43-55 were rejected as allegedly unpatentable over Applicants' admission that the method of using bupropion to treat smoking addiction and to aid in smoking cessation is known, in view of Coutts, R.T., and Baker, G.B. (1989) *Chirality* 1:99-120, ("Coutts"). This rejection is respectfully traversed.

As the Examiner is well aware, three basic criteria must be met to establish a case of *prima facie* obviousness: first, there must have been at the time of the invention a motivation to combine the references cited; second, the alleged prior art must teach or suggest all of the limitations of the claims alleged to be obvious; and third, there must have been at the time of the invention a reasonable expectation of success. *MPEP* § 2142. In contrast, an invitation to experiment or a contention that an invention is "obvious to try" does not render claims *prima facie* obvious, *see, e.g., Gillette Co. v. S. C. Johnson & Sons, Inc.*, 919 F.2d 720, 725 (Fed. Cir. 1990); *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988); *Jones v. Hardy,* 727 F.2d 1524, 1530; *Hybritech, Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1380 (Fed. Cir 1986) *cert. denied*, 480 U.S. 947 (1987) (prior art references were an invitation to try but did not show obviousness because they did not suggest how to accomplish the goal).

In particular, a rejection under § 103 is inappropriate when a general disclosure may stimulate the interest of a scientist, but does not contain sufficient teaching on how to obtain the desired result. *In re Eli Lilly & Co.*, 902 F.2d 943, 945 (Fed. Cir. 1990).

Contrary to the Examiner's allegation, the specification, on page 2, only discloses that racemic mixture of bupropion is commercially available for the treatment of depression and achieve smoking cessation. In fact, the specification clearly states that bupropion is commercially available as a racemic mixture. *See, e.g.*, specification at page 2, lines 3-13. There is no suggestion in the prior art, nor any admission by Applicants, regarding the use of the (+)-stereoisomer of bupropion as presently claimed.

Coutts does not remedy the deficiencies of the prior art in this regard. Coutts discloses that different enantiomers of a compound may possibly possess different pharmodynamic properties and that the desired therapeutic effect of the racemate may possibly reside in one enantiomer while possible undesirable toxic side effects may reside in the other enantiomer. *See, e.g.*, Coutts at page 99 in the abstract, page 100 col. 1, page 100 col. 2. However, Coutts in no way suggests that any prediction can be made about any given racemic drug in general, much less about bupropion in particular. This is clearly apparent from the repeated use of the word "may." *See, e.g.*, page 100, col. 1. This is further apparent from the substance of the article. For example, Coutts reports that the (+) and (-) enantiomers of 10-hydroxyamitriptyline have been determined to be "similar to one another in their abilities to inhibit NE and 5-HT uptake." Page 116, col. 1. Coutts further does not suggest which enantiomers (*e.g.*, the (-) or (+) enantiomer) of racemic drugs are preferable. This is because the optical rotation of compounds in general has no direct correlation with their pharmacological activity. For example, the (-) enantiomer of thalidomide has been reported to be toxic, while the (-) enantiomer of molindone is reportedly a more useful antidepressant than the (+) enantiomer. (Page 101, col. 1, and page 106, col. 1).

Coutts also makes it clear that even though individual enantiomers of racemic drugs may have different pharmacological properties, each of those enantiomers may have beneficial pharmacological properties. For example, Coutts discloses that while the (-) enantiomer of deprenyl is the active MAO-B inhibitor, (+)-deprenyl has "considerably greater

AMP-like action." Page 102, col. 2. Thus, Coutts suggests nothing specific about enantiomers of a racemic drug other than mere speculation that an enantiomer can be harmful or beneficial.

In sum, Coutts merely discloses that the enantiomers of some racemic compounds may have differing pharmacological activities. It does not suggest, however, that this is true of all racemic drugs, or that, in general, a particular optical isomer is preferred over another.

With regard to bupropion, Coutts states that racemic bupropion is used as an antidepressant, page 113 col. 1-2. Coutts notes that bupropion has a chiral center, but does not discuss whether a particular enantiomer of the drug has a desired therapeutic or undesired toxic effect. Indeed, Coutts does not even identify a specific enantiomer of bupropion that has a specific therapeutic effect.

Therefore, Coutts discloses that racemic bupropion is used as an antidepressant, and speculates that certain stereoisomers of certain drugs with chiral centers may have different therapeutic and toxic effects. Coutts is thus a general disclosure that may be of interest to scientists, but which does not contain a sufficient suggestion on how to obtain the invention recited by claims 16-29 and 43-55. Coutts is not even an invitation to experimentation, much less a suggestion plus expectation of success. Applicants therefore respectfully submit that the combination of Coutts with anything disclosed in the present application[1] at most only renders the claimed invention "obvious to try." *See, Eli Lilly & Co.*, 902 F.2d at 945. Accordingly, the cited art does not suggest that an optically pure (-) enantiomer of bupropion could be successfully used to treat smoking or nicotine addiction.

The Examiner also alleged, on page 5 of the Office Action, that it would have been obvious "to use the therapeutically active enantiomer of bupropion. One would be motivated by the desire to avoid the enantiomer which had the undesirable toxic effects."

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[1] Applicants respectfully note that it is improper to use their specification as prior art. *MPEP* §§ 2141.01 & 2142. Hindsight cannot be used to reject claims as obvious and such a rejection is akin to impermissible hindsight determination. *Id.* Consequently, when determining whether or not a claimed invention is obvious, one must cast his "mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999).

This statement rests on the assumption that, at the time of the claimed invention, those skilled in the art believed that adverse effects associated with racemic bupropion are due to only one of its enantiomers. But no art has been cited that supports such an assumption. Applicants are further not aware that such teaching existed in the public literature prior to the instant invention. However, if the Examiner knows that those skilled in the art did believe that adverse effects associated with racemic bupropion are due to only one of its enantiomers, Applicants respectfully request that she support the allegation made on pages 2-3 of the Final Office Action with an affidavit under 37 C.F.R. §1.104(d)(2).

But even assuming *arguendo* that, at the time of this invention, those skilled in the art did believe that one enantiomer of bupropion is less active than the other, or believed that one enantiomer induces adverse effects which the other does not, the claimed invention would still be patentable under 35 U.S.C. § 103. This is because a claimed invention cannot be found obvious under §103 simply because it would have been obvious to try to obtain it. *Hybritech*, 802 F.2d at 1380.

In view of the above, Applicants respectfully submit that a rejection of claims 16-29 and 43-55 under § 103 is inappropriate. *See, e.g., In re Eli Lilly & Co.*, 902 F.2d 943, 945 (Fed. Cir. 1990). Accordingly, Applicants respectfully request that the rejection of claims 16-29 and 43-55 under § 103(a) be withdrawn.

Conclusion

Applicants respectfully submit that the pending claims 16, 18-29, 43, 45-55, 79 and 80 are in condition for allowance.

No fee is believed to be due for this submission, except the fee for the Petition for Extension of Time submitted herein. Should any additional fee be required, however, please charge such fee to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date September 14, 2001

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Enclosures

APPENDIX A

The title has been has been replaced with the following new title:

-- Methods and Compositions for Treating Nicotine Addiction and Aiding in Smoking Cessation Using Optically Pure (-)-Bupropion –

Claims 1-15, 17, 30-42, 44 and 56-78 have been canceled, without prejudice and new claims 79 and 80 have been added.

The claims have been amended as follows:

16. (Amended) A method for treating nicotine addiction in a human suffering from nicotine addiction, which comprises administering to said human [suffering from nicotine addition,] a therapeutically effective amount of (-)-bupropion, or a pharmaceutically acceptable salt thereof, substantially free of its (+)-stereoisomer.

18. (Amended) The method of claim 16 [or 17] wherein (-)-bupropion is administered intravenously, transdermally, or orally.

19. (Amended) The method of claim 18 wherein (-)-bupropion is administered orally as a [table] tablet or a capsule.

23. (Amended) The method of claim 16 [or 17] wherein the amount of (-)-bupropion or a pharmaceutically acceptable salt thereof is greater than approximately 90 % by weight of the total amount of bupropion.

24. (Amended) The method of claim 16 [or 17] wherein the amount of (-)-bupropion or a pharmaceutically acceptable salt thereof is 99 % or more by weight of the total amount of bupropion.

25. (Amended) The method of claim 16 [or 17] wherein the amount of (-)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (+)-stereoisomer, is administered together with a pharmaceutically acceptable carrier.

26. (Amended) The method according to claim 16 [or 17] wherein (-)-bupropion is administered as the hydrochloride salt.

27. (Amended) The method of claim 16 [or 17] wherein (-)-bupropion is administered in a sustained or controlled release formulation.

28. (Amended) The method of claim 16 [or 17] wherein said nicotine addiction is an addiction to smoking, or chewing tobacco.

29. (Amended) The method of claim 16 [or 17] wherein said administration is made one to four times a day.

43. (Amended) A method for aiding smoking cessation [by] <u>in</u> a human <u>who smokes</u>, which comprises administering to said human [who smokes] a therapeutically effective amount of (-)-bupropion, or a pharmaceutically acceptable salt thereof, substantially free of its (+)-stereoisomer.

45. (Amended) The method of claim 43 [or 44] wherein (-)-bupropion is administered intravenously, [by bolus injection,] transdermally, [intrathecally,] or orally.

47. (Amended) The method of claim 43 [or 44] wherein the amount administered is from about 10 mg to about 750 mg.

50. (Amended) The method of claim 43 [or 44] wherein the amount of (-)-bupropion or a pharmaceutically acceptable salt thereof is greater than approximately 90 % by weight of the total amount of bupropion.

51. (Amended) The method of claim 43 [or 44] wherein the amount of (-)-bupropion or a pharmaceutically acceptable salt thereof is 99 % or more by weight of the total amount of bupropion.

52. (Amended) The method of claim 43 [or 44] wherein the amount of (-)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (+)-stereoisomer is administered together with a pharmaceutically acceptable carrier.

53. (Amended) The method according to claim 43 [or 44] wherein (-)-bupropion is administered as the hydrochloride salt.

54. (Amended) The method of claim 43 [or 44] wherein (-)-bupropion is administered in a sustained or controlled release formulation.

55. (Amended) The method according to claim 43 [or 44], wherein said administration is made one to four times per day.

79. (New) The method of claim 45, wherein the (-)-bupropion is administered by bolus injection.

80. (New) The method of claim 45, wherein the (-)-bupropion is administered intrathecally.

APPENDIX B

The pending claims, after entry of the present amendment, are as follows:

16. A method for treating nicotine addiction in a human suffering from nicotine addiction, which comprises administering to said human a therapeutically effective amount of (-)-bupropion, or a pharmaceutically acceptable salt thereof, substantially free of its (+)-stereoisomer.

18. The method of claim 16 wherein (-)-bupropion is administered intravenously, transdermally, or orally.

19. The method of claim 18 wherein (-)-bupropion is administered orally as a tablet or a capsule.

20. The method of claim 18 wherein the amount administered is from about 10 mg to about 750 mg.

21. The method of claim 19 wherein the amount administered is from about 50 mg to about 600 mg.

22. The method of claim 20 wherein the amount administered is from about 60 mg to about 450 mg.

23. The method of claim 16 wherein the amount of (-)-bupropion or a pharmaceutically acceptable salt thereof is greater than approximately 90 % by weight of the total amount of bupropion.

24. The method of claim 16 wherein the amount of (-)- bupropion or a pharmaceutically acceptable salt thereof is 99 % or more by weight of the total amount of bupropion.

25. The method of claim 16 wherein the amount of (-)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (+)-stereoisomer, is administered together with a pharmaceutically acceptable carrier.

26. The method according to claim 16 wherein (-)-bupropion is administered as the hydrochloride salt.

27. The method of claim 16 wherein (-)-bupropion is administered in a sustained or controlled release formulation.

28. The method of claim 16 wherein said nicotine addiction is an addiction to smoking, or chewing tobacco.

29. The method of claim 16 wherein said administration is made one to four times a day.

43. A method for aiding smoking cessation in a human who smokes, which comprises administering to said human a therapeutically effective amount of (-)-bupropion, or a pharmaceutically acceptable salt thereof, substantially free of its (+)-stereoisomer.

45. The method of claim 43 wherein (-)-bupropion is administered intravenously, transdermally, or orally.

46. The method of claim 45 wherein (-)-bupropion is administered orally as a tablet or a capsule.

47. The method of claim 43 wherein the amount administered is from about 10 mg to about 750 mg.

48. The method of claim 47 wherein the amount administered is from about 50 mg to about 600 mg.

49. The method of claim 48 wherein the amount administered is from about 60 mg to about 450 mg.

50. The method of claim 43 wherein the amount of (-)-bupropion or a pharmaceutically acceptable salt thereof is greater than approximately 90 % by weight of the total amount of bupropion.

51. The method of claim 43 wherein the amount of (-)-bupropion or a pharmaceutically acceptable salt thereof is 99 % or more by weight of the total amount of bupropion.

52. The method of claim 43 wherein the amount of (-)-bupropion or a pharmaceutically acceptable salt thereof, substantially free of its (+)-stereoisomer is administered together with a pharmaceutically acceptable carrier.

53. The method according to claim 43 wherein (-)-bupropion is administered as the hydrochloride salt.

54. The method of claim 43 wherein (-)-bupropion is administered in a sustained or controlled release formulation.

55. The method according to claim 43, wherein said administration is made one to four times per day.

79. The method of claim 45, wherein the (-)-bupropion is administered by bolus injection.

80. The method of claim 45, wherein the (-)-bupropion is administered intrathecally.